Feasibility, safety, and impact of the RTS,S/AS01$_E$ malaria vaccine when implemented through national immunisation programmes: evaluation of cluster-randomized introduction of the vaccine in Ghana, Kenya, and Malawi.

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Summary [590 words]

Background RTS,S/AS01$_E$ malaria vaccine (RTS,S) was introduced by national immunization programmes in Ghana, Kenya, and Malawi in 2019 in large-scale pilot schemes. Prospective evaluations were conducted to address questions about feasibility and effectiveness, and to assess safety signals that had been observed in the phase 3 trial, before recommending wider use. One-hundred-fifty-eight clusters (66 districts in Ghana; 46 sub-counties in Kenya; and 46 groups of immunization clinic catchment areas in Malawi) were randomized to early or delayed introduction of RTS,S, with three doses to be administered between the ages of 5 and 9 months and a fourth dose at approximately 2 years. Primary outcomes of the evaluation, planned over 4 years, were mortality from all causes except injury, hospital admission with severe malaria, and, with respect to safety, hospital admission with meningitis or cerebral malaria, and deaths in girls compared to boys, and, for feasibility, vaccination coverage. Preliminary findings contributed to the World Health Organisation's recommendation in 2021 for widespread use of RTS,S in areas of moderate to high malaria transmission.

Methods Mortality surveillance was undertaken in children aged 1-59 months throughout the pilot areas. Surveillance for meningitis and severe malaria was established in 8 sentinel hospitals in Ghana, 6 in Kenya, and 4 in Malawi. Vaccine uptake was measured in surveys of children aged 12-23 months about 18 months after vaccine introduction. Sufficient data had accrued after 24 months to evaluate each of the safety signals and the impact on severe malaria in a pooled analysis of the data from the three countries. We estimated incidence rate ratios (IRR's) by comparing the ratio of the number of events in children age-eligible to have received at least one dose of the vaccine (for safety outcomes), or age-eligible to have received three doses (for impact), to that in non-eligible age groups, between implementation and comparison areas. To determine if there was evidence of a difference between girls and boys in the vaccine's impact on mortality, the female: male mortality ratio in age groups eligible to receive the vaccine relative to the ratio in non-eligible children was compared between implementation and comparison areas.

Findings By April 30 2021, 652,673 children had received at least one dose of RTS,S and 494,745 children had received three doses. Coverage of the first dose was 76% in Ghana, 79% in Kenya, and 73% in Malawi, and of the third dose, 66%, 62% and 62%, respectively. A total of 26,285 children aged 1-59 months were admitted to sentinel hospitals and 13,198 deaths were reported through mortality surveillance. Among children eligible to have received at least one dose of RTS,S, there was no evidence of an excess of meningitis or cerebral malaria cases (IRR (implementation:comparison areas) for hospital admission with meningitis was 0·63, 95% CI 0·22,1·79 and with cerebral malaria 1·03, 95% CI 0·61,1·74), and the impact of RTS,S introduction on mortality was similar for girls and boys (relative mortality ratio 1·03, 95% CI 0·88,1·21). Among children eligible for three vaccine doses, RTS,S introduction was associated with a 32% (95% CI 5%, 51%) reduction in hospital admission with severe malaria, and a 9% (95% CI 0%, 18%) reduction in all-cause mortality excluding injury.

Interpretation In the first two years of implementation of RTS,S, the three primary doses were effectively deployed through national immunisation programmes, there was no evidence of the safety signals that had been observed in the phase 3 trial, and introduction of the vaccine was associated with substantial reductions in hospital admission with severe malaria. Evaluation continues to assess the impact of 4 doses of RTSS.

Research in context

Evidence before this study: We searched the PubMed database from January 1, 2009 to October 7, 2022 for Phase 2 or 3 RTS,S/AS01 clinical trials and systematic reviews with the search terms ((“RTS,S/AS01”[All Fields] AND (“safety”[All Fields] OR “meningitis”[All Fields] OR “cerebral malaria”[All Fields] OR “feasibility”[All Fields] OR “coverage”[All Fields] OR “mortality”[All Fields] OR “impact”[All Fields] OR “cases-averted”[All Fields] OR “deaths-averted”[All Fields]))); 25 publications were identified describing data from 14 trials including one large multi-centre phase 3 trial. All the trials found RTS,S/AS01 had a satisfactory safety profile, but in the multi-centre phase 3 trial there were three safety signals- an excess of meningitis cases and of cerebral malaria cases in RTS,S/AS01 recipients, and among girls, more deaths in those who received RTS,S/AS01 than controls. These safety signals were unexplained and had no temporal association with vaccination, and were not detected in a subsequent analysis of pooled Phase 2 data. In the multi-centre phase 3 trial, among children who received three vaccine doses the incidence of clinical malaria and of severe malaria were reduced by 56% and 47% respectively over one year, and in children who received a fourth dose (18 months after the third dose), by 39% and 32% respectively over four years. It appeared that the fourth vaccine dose was necessary to reduce a child’s overall risk of severe malaria over the 4 years of the trial, although there was uncertainty regarding this conclusion. For every 1000 children vaccinated with 4 doses, a total of 1774 cases of malaria and 40 hospital admissions due to malaria were averted over about 4 years, and models predicted the vaccine would be cost effective especially in higher transmission settings. Clinical trials of seasonal vaccination with RTS,S/AS01 (3 primary doses followed by two annual booster doses) showed vaccine efficacy over 3 years of 63% against clinical malaria, 70% against hospital admission with severe malaria, and 73% against deaths from malaria, in children receiving Seasonal Malaria Chemoprevention.

Added value of this study: RTS,S/AS01$_E$ is the world’s first licensed malaria vaccine. This is the first study to evaluate a malaria vaccine when introduced as part of national immunisation programmes. A robust evaluation of feasibility, safety, and impact was undertaken using standardized methods of surveillance in implementation and comparison areas chosen by randomization. Results after 2 years show that over 70% of 1-yr-old children had received a first dose of the vaccine, with no evidence of the safety signals that had been observed in the earlier phase 3 clinical trial. In the age groups of children who would have been eligible to have received three doses of the malaria vaccine, introduction of the vaccine was associated with a reduction in hospital admissions with severe malaria by a third, and a reduction in child deaths of any cause excluding injury of 9%. The impact was realised in the context of moderate coverage and during the COVID-19 pandemic.

Implications of all the available evidence: Implementation of the RTS,S/AS01$_E$ malaria vaccine into routine immunization programmes can have a significant impact in reducing severe illness and deaths in young children caused by *P. falciparum* malaria. The evidence from our study and those of others show that wider introduction of the vaccine should be accelerated as a matter of urgency. WHO recommended in 2021 that the vaccine should be provided for children in all regions with moderate to high malaria transmission. GAVI, The Vaccine Alliance, has added malaria vaccination to its portfolio, but supplies of the RTS,S vaccine are projected to fall far short of the number of doses needed. The evidence from our study and those of others show that efforts

to increase malaria vaccine supply and widen its introduction should be accelerated as a matter of urgency.

Introduction [505 words excluding citation numbers]

There were an estimated 247 million malaria cases and 619,000 malaria deaths worldwide in 2021; the vast majority occurred in young children in sub-Saharan Africa (1). The World Health Organization (WHO) estimates of key indicators of global malaria burden have not improved since 2015, attributed in part to rising insecticide resistance, humanitarian crises, and other health system challenges (1). In areas with high malaria burden, transmission is so intense that children are still at appreciable risk even when using all recommended interventions (2). Additional malaria control tools are therefore urgently needed. In October 2021, WHO recommended that the RTS,S/AS01$_E$ malaria vaccine (henceforth RTS,S) should be used in all areas with moderate or high transmission to prevent *P. falciparum* malaria in young children (3). We present results from the first two years of large-scale pilot implementation of the vaccine in Ghana, Kenya, and Malawi which contributed to this recommendation.

In 2015, the European Medicines Agency reviewed data from the multi-centre phase 3 trial of RTS,S (4), and earlier studies, and gave a positive scientific opinion under Article 58, for both age groups studied in the phase 3 trial, infants aged 6-14 weeks and children aged 5-17 months (5, 6). WHO then considered the potential use of RTS,S and recommended large-scale pilot implementation of the 4-dose regimen in children aged at least 5 months at first dose, in settings with moderate to high malaria transmission. The pilot was designed to assess the feasibility of implementing 4-doses of the vaccine, in a schedule beyond regular contacts of the Expanded Program on Immunization (EPI); the vaccine's safety; and the impact of vaccine introduction on mortality and on the incidence of hospital admission with severe malaria (8). The vaccine was not recommended in the 6-14-week age group due to lower efficacy in this group in the phase 3 trial (7). With respect to safety, the focus was on three signals seen in the phase 3 trial, none of which were temporally associated with vaccination: an excess of meningitis and cerebral malaria cases in recipients of RTS,S, and an interaction between sex and vaccine group (14). Health authorities in Ghana, Kenya, and Malawi authorised use of the vaccine in pilot areas in 2018, and the national EPI in each country conducted a phased introduction of the vaccine in pilot areas in April (Ghana and Malawi) and September (Kenya), 2019. The evaluation was planned over 4 years, with primary analysis of the safety signals and the initial impact on the incidence of hospital admission with severe malaria planned at 24 months, as it was anticipated that there would be sufficient data by that time to inform a recommendation for wider use of the vaccine (7). Here, we present the evaluation of feasibility, safety, and impact of RTS,S, with a focus on the primary three doses, based on data accrued over 24 months up to 30 April 2021. Evaluation will continue for 46 months in each country total providing information on uptake and impact of four doses and the overall impact on mortality.

Methods [1580 words]

Selection of evaluation areas

Participating countries were selected among applicant countries based on having regions with moderate-to-high year-round malaria transmission and good coverage of childhood vaccinations and core malaria interventions (9). Surveillance for child mortality was strengthened throughout these pilot regions; hospital-based surveillance for severe malaria and other conditions was limited to part of each region served by selected sentinel hospitals where clinical and laboratory

investigations were strengthened. Further description, and maps of pilot regions, are provided in the Supplement (SS1).

Randomization

Within the pilot region in each country, the EPI defined clusters, each with a total population of about 100,000 and about 4,000 births per year. A total of 158 clusters were randomized (66 districts in Ghana; 46 sub-counties in western Kenya; and 46 groups of immunization clinics and their associated catchment areas in Malawi). An independent statistician assisted the EPI to randomize clusters to introduce RTS,S in 2019 (implementing areas) or to delay introduction (comparator areas) (SS2). Constrained randomization in each country aimed to balance implementing and comparator areas with respect to the number of infants surviving to 12 months, malaria parasite prevalence (10), EPI coverage (pentavalent dose 3 and measles dose 1), and number of hospitals, health centres, and dispensaries. Additional balance criteria within areas defined for hospital surveillance were the number of sentinel hospitals and access to hospital as measured by estimates of the number of patients admitted to hospitals from each cluster prior to vaccine introduction, but in Kenya these balance criteria resulted in overly restricted allocation options and were relaxed. A community representative in each country selected the final allocation at random from a list of approximately balanced randomization options. Table 1 shows the characteristics of implementation and comparison areas prior to RTS,S introduction.

Surveys to monitor vaccine uptake

Large, representative household surveys were conducted in implementing areas of each country at baseline and after about 18 months to measure coverage of EPI vaccines including RTS,S, use of long-lasting insecticide-treated bednets (LLINs), to ask about care-seeking for fever, and to determine the prevalence of *P. falciparum* malaria using a malaria rapid diagnostic test. Caregivers were asked about the child's vaccination history and vaccination dates were recorded from the home-based vaccination record, if available. Survey design and conduct are described in SS3.1.

Sentinel hospital surveillance

Sentinel referral hospitals were selected (8 in Ghana, 6 in Kenya, 4 in Malawi) which had a high volume of paediatric admissions and were able to collect and analyse cerebrospinal fluid (CSF) for diagnosis of meningitis and cerebral malaria. Laboratory capacity was strengthened, and hospital staff supported to undertake clinical investigation using standardized case definitions for malaria, severe malaria, cerebral malaria, and meningitis (Table S2) through training and supervision, quality assurance, and provision of lumbar puncture kits and laboratory reagents (SS3.2). Staff were trained to extract data on patient age, usual residence, vaccination status, clinical history and examination, laboratory results, and discharge diagnosis from patient case notes for all admitted children aged 1–59 months. For cases with suspected meningitis or cerebral malaria, lumbar puncture (LP) was performed, CSF collected and analysed locally to determine clinical care, and an aliquot sent for pathogen genotyping by polymerase-chain reaction (PCR) at reference laboratories.

Mortality surveillance

Surveillance for mortality was established in the community throughout the implementation and comparison areas. When a child death was reported, an interviewer visited to confirm place of

usual residence, sex, age at death, and complete a verbal autopsy (VA) using the WHO VA instrument to evaluate cause of death (SS3.3). RTS,S vaccine status was recorded from the child's vaccination book (home-based record, HBR) and/or by maternal recall. Cause of death was ascertained from Inter-VA analysis (or, for deaths in a health facility in Malawi, from the death notification form).

Vaccine introduction

In Ghana and Kenya, doses were scheduled at 6,7,9, and 24 months of age, and in Malawi at 5,6,7, and 22 months. The revised EPI schedules for each country are shown in Figure S2. At the time of RTSS introduction, the first dose could be given up to 7 months of age in Ghana, up to 11 months in Kenya, and not above 5 months of age in Malawi. The upper age limits for the first dose in Ghana and Malawi were later modified to up to 11 months. The vaccine was introduced in Malawi on 23 April 2019, in Ghana on 30 April 2019, and in Kenya on 13 September 2019 (SS4).

Statistical methods

Primary outcomes:

Primary outcomes were, with respect to feasibility, vaccination coverage; for safety, hospital admission with meningitis or cerebral malaria and death due to any cause excluding injury compared between girls and boys; and with respect to impact, mortality from all causes except injury, and hospital admission with severe malaria.

Meningitis was defined as probable meningitis based on macro-and micro-scopic examination of CSF or as confirmed meningitis based on a positive CSF PCR result for bacterial or viral aetiology, in patients with suspected meningitis. Cerebral malaria was defined as *P. falciparum* positive (antigenaemia detected by RDT, or parasitaemia by microscopy if an RDT was not done) with impaired consciousness (Glasgow coma score <11 or Blantyre coma score <3 or assessed as P or U on AVPU score [Alert, Voice, Pain, Unresponsive]) in a patient that did not meet any meningitis definition (Table S2). Severe malaria was defined as admission to hospital with a positive malaria test, with severe anaemia, respiratory distress, impaired consciousness (and not positive for meningitis), or convulsions (and not positive for meningitis) (Table S2). Although all cerebral malaria cases, and severe malaria cases with impaired consciousness or convulsions, also met the criteria for suspected meningitis, not all had LP; but if LP was performed and CSF findings were consistent with probable or confirmed meningitis, those cases were excluded. Additional analyses were performed for severe malaria and cerebral malaria excluding cases that met the definition of suspected meningitis but for which meningitis status could not be determined (e.g., due to LP not performed) (Table S2; Figure S8 & S9). All events occurring from the first date of vaccine implementation in each country (23 April 2019, 30 April 2019, 13 September 2019 in Malawi, Ghana and Kenya respectively), up to 30 April 2021, in children living in the pilot areas (for mortality) or living in defined hospital surveillance areas (for hospital outcomes), were included.

Analysis methods:

Coverage estimates were obtained using standard methods for surveys, described in the Supplement (p30-31).

For safety analyses, rate ratios were estimated comparing incidence between RTS,S implementation and comparison areas among age groups eligible to receive the first dose of RTS,S vaccine (RTS,S-1), and for impact analyses, among age groups eligible to have received a third dose (RTS,S-3). The methods are detailed in the Supplemnent, p28-32. Stata version 15 (Statacorp, College Station, Texas) was used for the analyses. Rate ratios were estimated as a double-ratio of event counts (11), comparing the ratio of events between eligible and non-eligible age groups in RTS,S implementation areas, with that in comparison areas (SS5, Figure S3). Eligibility was defined according to the child's age at admission or death (determined by date of birth or recalled age), the date of vaccine introduction and the country-specific schedule (Figure S3). Children just above the eligible age limit, by up to 2 months, were excluded. Pooled estimates of rate ratios were obtained by weighting log country estimates by the inverse of the variance (SS5). The female:male mortality ratio in vaccine-eligible age groups was compared between implementation and comparison areas similarly, using data in non-eligible boys and girls as auxiliary variables. Further details of the analysis methods are provided in the Supplement pp.28-32.

We estimated the number of events required for 90% power to detect a difference between implementation and comparison areas, for each safety outcome, if the safety signal occurred at the level observed in the phase 3 trial, after allowing for dilution of effects due to incomplete RTS,S coverage and contamination (SS5.2, p31). With respect to mortality, the evaluation was similarly powered to detect a difference in impact of RTS,S between girls and boys, allowing for dilution. We also estimated the number of severe malaria admissions required for 90% power to detect a reduction if RTS,S effectiveness was similar to the efficacy in the phase 3 trial, allowing for dilution. We estimated that sufficient events of each safety outcome, and of severe malaria, would have accrued 24 months after the start of the evaluation and planned primary analyses of these outcomes at this time. Analyses followed a predefined analysis plan (12) and framework for policy making (7), which specified that a broader recommendation on RTS,S could be made if the safety signals were not replicated, and the data on severe malaria and mortality were consistent with a benefit, recognizing that primary analysis of the impact on mortality, and assessment of the value of the 4th dose, would be done at the end of the 4 year evaluation.

Consent of parent/guardian was sought for data collection following approval by the institutional review boards of the evaluation partners' institutions and WHO (SS6). Sentinel surveillance in Kenya used an established routine system and parental consent was only obtained for CSF storage (13). The evaluation is registered on ClinicalTrials.gov (NCT03806465) as an observational study. An independent data safety monitoring board, and the MVIP Programme Advisory Group, provided oversight.

Role of the funding source
The funders of the study did not contribute to the study design, data collection, data analysis, data interpretation, or writing of the report.

Results [1328 words]
Coverage of basic vaccines, use of LLINs, and malaria prevalence before RTS,S introduction
In implementation areas surveyed before RTS,S was introduced, coverage of the third dose of pentavalent (DPT+Hib+HepB) vaccine in Ghana, Kenya and Malawi was 93%, 92%, and 88% respectively among children aged 12-23 months. Coverage of the first dose of measles-containing

vaccine (MCV) was 90%, 85% and 85% among children aged 12-23 months; the coverage of MCV2 was 83%, 48%, and 63% among children 24-35 months of age in Ghana, Kenya, and Malawi, respectively. Coverage of these vaccines in comparison areas was similar to that in implementation areas. Use of LLINs among children 5-48 months of age was 63%, 86% and 90% in implementation areas in Ghana, Kenya and Malawi, and 60%, 89% and 92% in comparison areas. The prevalence of *P. falciparum* by RDT in children aged 5-48 months was 21%, 26%, and 28% in implementation areas and 20%, 19%, and 17% in comparison areas, in Ghana, Kenya and Malawi respectively (Table 1).

Uptake of RTS,S vaccine, the use of other interventions, and care-seeking behaviour following RTS,S introduction

By 30 April 2021, a total of 652,673 children had received their first dose, 238,318 in Ghana, 187,857 in Kenya and 226,498 in Malawi. A total of 494,745 children had received their third dose (173,552 in Malawi, 200,398 in Ghana, and 120,795 in Kenya) and 79,523 children had received their fourth dose (35,209 in Ghana, 10,805 in Kenya, 33,509 in Malawi). Approximately 18-months post-introduction, among children aged 12-23 months surveyed in implementation areas in Ghana, 76% (95%CI 72%,79%) had received their first dose of RTS,S and 66% (95%CI 62%,71%) the third dose; in Kenya, 79% (95%CI 74%,83%) and 62% (95%CI 58%,67%) had received the first and third dose respectively, while in Malawi, the percentages were 73% (95%CI 68%,77%) and 62% (95%CI 57%,67%) respectively. In each country, vaccine uptake was similar in girls and boys and across wealth rankings except in Kenya where children in the upper third for wealth were more likely to have received three doses of RTS,S than children in the lower third (Figure 1B). In each country, children who slept under a LLIN were more likely to have received three doses of RTS,S than children who did not sleep under a LLIN (Figure 1B). There was no evidence that introduction of RTS,S affected uptake of other vaccines, vitamin A, or use of LLINs, or care-seeking for fever (Figure 2). Similar results were observed in sentinel hospital surveillance areas (Figure S4).

Hospital surveillance

A total of 31,072 children aged 1-59 months were admitted to sentinel hospitals from the date of RTS,S introduction up to 30 April 2021, of whom 29,356 resided in defined hospital surveillance areas, had parental consent, and had a date of birth or age documented to determine vaccine eligibility (Figure S5). Among patients with fever or history of fever (22,463/27,596 [81%]), 94% (21,036/22,463) had a malaria test result. A total of 4964 patients from implementation areas were eligible to receive their first RTS,S dose (including 3570 who were eligible to have received three doses), 8231 were not eligible (too young or too old when RTS,S was introduced), and 687 were excluded from analyses as they were just too old for RTS,S by a margin of up to 2 months. Corresponding numbers from comparison areas were 5239, 3887, 7851, and 624 respectively (Figure S5). The incidence rate ratio (IRR) for conditions of any cause excluding patients with malaria infection, anaemia, or meningitis, among children eligible for their first dose of RTS,S was 1·04 (95%CI 0·93, 1·17), and among those eligible to have received 3 doses was 1·04 (95%CI 0·92, 1·17), showing that implementation and comparison areas were comparable with respect to admission with conditions that were unlikely to be affected by the malaria vaccine (Figures 3 and 4). Flowcharts detailing analysis populations, case numbers for hospital surveillance outcomes by area and eligibility, and exclusions due to missing data, are given in Figures S7-S9.

Mortality surveillance
A total of 14,663 deaths in children aged 1-59 months were reported to 30th April 2021 with 14,660 ascertained as living in MVPE areas. Of the 5220 in eligible age groups, 5035 (96%) had verbal autopsy completed or facility death notification obtained. A cause of death (categorized as due to injury, or other causes) was established for 4,520/5,035 (90%). A flowchart detailing analysis populations by area and eligibility, and exclusions due to missing data, is given in Figure S6.

Safety outcomes amongst children eligible for at least one dose of RTS,S
Meningitis: There were 4136 admissions (eligible and non-eligible age groups) with suspected meningitis. Lumbar punctures were performed in 2570/4136 (62%), for which 2138/2570 (83%) had a white cell count recorded and 2438 (95%) had the macroscopic appearance of the CSF recorded; PCR results were obtained for 2123 (83%). Criteria for probable or confirmed meningitis were met in 132 patients, 72 from implementation areas (28 in age groups eligible to receive RTS,S-1), and 60 from comparison areas (25 in age groups eligible to receive RTS,S-1) (Figure S7). The IRR comparing incidence of probable or confirmed meningitis in eligible age groups between RTS,S and comparison areas was 0·63 (95% CI 0·22, 1·79) (Figure 3). Reasons why LPs were not done (Table S5), and sensitivity analyses using imputed data for those without LP (which showed similar results), are detailed in Table S6 (p.40). PCR results identified vaccine-preventable bacteria (*Haemophilus influenzae* type b, or vaccine serotypes of *Streptococcus pneumoniae*) in 15% (8/54) of samples from confirmed meningitis cases (Table S7).

Cerebral malaria: There were 1423 cases of severe malaria among children eligible to have received RTS,S-1, 568 from implementation areas, of which 52 had cerebral malaria, and 855 from comparison areas, 56 with cerebral malaria (Figure S8). The IRR comparing incidence of cerebral malaria between implementation and comparison areas was 1·03 (95%CI 0·61, 1·74), Figure 3. When cases of unknown meningitis status were excluded, there were 59 cases (27 from implementation and 32 from comparison areas), the IRR was 0·82 (95% CI 0·39, 1·72) (Figure 3).

Mortality in girls and boys: There were 4748 deaths (excluding those due to injury) in children eligible for RTS,S-1, 2386 from implementation areas (1166 boys and 1220 girls) and 2362 from comparison areas (1097 boys and 1265 girls) (Figure S6). There were 8450 deaths in non-eligible age groups (2115 boys and 2304 girls from implementation areas and 1882 boys and 2149 girls from comparison areas). The mortality ratio associated with RTS,S introduction (both sexes combined) was 0·93 (95% CI 0·84, 1·02), with no evidence of a difference between girls and boys. The mortality ratio in girls was 0·95 and in boys 0·91 (Figure 3), the relative mortality ratio (girls:boys) was 1·03 (95% CI 0·88, 1·21, p = 0·71). Tables S8 & S9 give country-specific results.
Impact among children eligible to have received three doses of RTS,S
Among children eligible for RTS,S-3 there was a 32% reduction in hospital admissions with severe malaria, with 427 in the intervention areas and 697 from comparison areas, IRR 0·68 (95%CI 0·49,0·95). There was no evidence that impact on severe malaria differed between cerebral and other types of severe malaria (interaction p-value 0.10). Within the severe malaria subset analysis excluding cases also meeting the criteria for suspected meningitis but with unknown meningitis status, the number of cases was 333 and 557, IRR 0·63 (95%CI 0·44,0·91), a 37% reduction (with no interaction by type of severe malaria, p=0.88). There was a total of 3436 hospital admissions for any cause from implementation areas and 3767 from comparison areas (Figure S9), IRR 0·91 (0·80, 1·03). The number of admissions with a positive malaria test was 1163 and 1652 from each

area, IRR 0·78 (95%CI 0·66, 0·94). The number of deaths, excluding those due to injury, was 1589 and 1631 in implementation and comparison areas, IRR 0·91 (95%CI 0·82, 1·00) (Figure 4). There was no evidence that the impact on mortality differed between girls and boys (interaction test p=0·81). Tables S8-S11 give country-specific results.

Discussion [1204 words]

The comprehensive evaluation reported in this paper was planned to assess effectiveness and resolve specific safety signals of RTS,S, the world's first malaria vaccine, to inform decisions about wider scale-up of the vaccine as soon as was possible. By April 2021, about 1.8 million doses of RTS,S had been administered through routine child immunization clinics. By 18 months after introduction, over 70% of 1-yr-olds had received their first dose and over 60% had received three doses, with similar coverage across socioeconomic groups and in boys and girls. By 24 months after introduction in Malawi and Ghana, and after 19 months in Kenya (which started later than the other two countries), no evidence was found of the safety signals that had been observed in the phase 3 trial (4, 14), and among the cohorts of children who could have received 3 doses of the vaccine there was a reduction in hospital admissions with severe malaria by 32%. Total hospital admissions of any cause were 9% lower in implementation areas, and deaths of all causes (excluding those due to injury) were also 9% lower. These values are consistent with the important contribution severe malaria makes to admissions to hospital and to deaths at home or in hospital in these populations (1). Findings from this study were reported to WHO between July and September 2021 (15) and constituted critical evidence that informed WHO's recommendation on 6 October 2021 that the RTS,S vaccine should be widely implemented in sub-Saharan Africa and in other regions with moderate to high *P. falciparum* malaria transmission (16) to prevent malaria in young children. The evaluation will continue to assess the uptake and effectiveness of the full 4-dose schedule of RTSS, including impact on mortality over a total period of 46 months since first introduction in each country.

For this evaluation, standardised surveillance methods were employed, diagnostic procedures in hospital were strengthened, and community mortality surveillance strengthened throughout the pilot study regions. Ministries of Health chose implementation areas using randomization to ensure robustness of the evaluation. Vaccine delivery was independently assessed through large household surveys.

The over 60% coverage of the primary three doses of the vaccine within 18 months of vaccine introduction is notable given the need for additional visits outside the usual EPI schedule and the challenges of maintaining vaccine delivery during the COVID-19 pandemic. This success reflects the commitment of health staff, and positive caregiver perceptions of the vaccine as noted in qualitative observations of caregiver cohorts reported elsewhere (17). Caregivers increasingly expressed positive attitudes and trust in RTS,S during the study period, having perceived health benefits of the vaccine in their children and their community. However, coverage of the first dose of RTS,S was lower than coverage of the first dose of measles vaccine, indicating missed opportunities to receive RTS,S. Our findings reflect the effectiveness of the primary 3 doses, as few children had received dose 4 by the time of our analysis (18, 19, 20, 21).

We found no evidence that introduction of RTS,S was associated with an increase in cases of meningitis or cerebral malaria, or deaths in girls. safety signals that had been observed in the phase 3 trial. Our evaluation was powered to detect these signals if they had occurred during the pilot implementation, taking into account the fact that the effects would have been diluted by incomplete coverage and contamination.

The observed impact of RTS,S on hospital admission with severe malaria is consistent with impact that would be expected based on the efficacy observed in the phase 3 trial given the level of uptake of the vaccine in implementation areas. In the phase 3 trial, efficacy against clinical malaria wanes over time, 68% in the first 6 months following dose 3, and 55% during the first 12 months. Many of the children who would have received 3 doses, and contributed person time in our evaluation, would have benefited during that time from the relatively high efficacy in the months following the third dose.

There was no evidence that RTS,S introduction influenced the use of LLINs by children, health-seeking behaviour for fever, or the uptake of other vaccines. Although the lack of a negative impact is reassuring, a positive impact of the specific health worker training (to look for missed vaccinations at every visit, to tell parents to return if children had a fever, and to reinforce the message that LLINs be used every night) might have been anticipated. Coverage of RTS,S was higher among children using LLINs than children not using LLINs but a substantial proportion of children not using LLINs did receive RTS,S, thereby increasing the proportion of children with access to some form of malaria prevention. The increase was especially marked in Ghana and Malawi where in the midline surveys LLIN use was lower than in Kenya.

Limitation

Several factors could have diluted estimates of safety signals. However, the fact that the impact observed against severe malaria was consistent with the expected impact, and the consistent point estimates for other impact outcomes, argue against dilution effects having been significantly under-estimated, and this is supported by updated dilution factors calculated using coverage survey data (Supplement S5.2.3). For cerebral malaria, confidence intervals were relatively wide, but the data were consistent with no excess of cases and we found no evidence that impact differed from other forms of severe malaria. Confounding, whereby malaria vaccine uptake is associated with underlying risks of malaria, meningitis or mortality, could influence estimates of effects. However, we found no association between EPI coverage and malaria prevalence during baseline surveys. With respect to meningitis, although children who received the malaria vaccine were more likely to have previously received pneumococcal vaccine and Hib vaccine than children who did not receive the malaria vaccine, this was unlikely to have masked an effect of the malaria vaccine on meningitis risk because vaccine serotypes of Hib and pneumococcus were relatively uncommon when CSF samples were investigated by PCR.

Despite efforts to strengthen clinical investigation, diagnostic performance was imperfect, and events could have been missed or misclassified (22). It is also likely that deaths have been under-reported through the mortality surveillance system. However, the analytical approach aimed to control for differences in completeness of investigation and detection, and for imbalance in access to hospital by using data on the same outcomes in non-eligible age groups in each cluster as an auxiliary variable. In addition, in the case of meningitis, sensitivity analysis using imputed values

suggested no bias due to missing LP results. The analytic approach avoided reliance on person time denominators which can be difficult to estimate reliably, especially for hospital outcomes where catchment populations and access to hospital may be poorly defined, and also improved statistical efficiency compared to standard statistical methods for outcomes with highly variable counts among clusters (11).

This evaluation shows that RTS,S can be effectively deployed through national immunisation programmes, and with no evidence of the safety signals that had been reported from the phase 3 trial, leading to substantial reductions in severe illness caused by malaria and to mortality reductions. Although now recommended by WHO, supply of the RTS,s vaccine is forecast to fall far short of demand for the next 4-6 years (23). Our findings highlight the urgency to increase supplies of this or other safe and effective malaria vaccines, and to ensure resources to introduce and implement malaria vaccines effectively.

Contributors:

KPA, ASam, DM led the evaluation in Ghana, Kenya and Malawi. DS, PM, MH designed the evaluation. AC, AH, AKa, AKT, AKu, AO, ASam, ASar, AW, BO, BS, DAG, DAk, DAn, DM, EAa, EAw, EM, EOL, FA, FB, GO, HMa, HMs, IN, JC, JJ, JS, KK, KMa, KPA, LM, LO, MB, ME, MM, MO, MZ, NC, NW, OO, PBu, PW, SAE, SAk, SK, TA, TG, TK, TM, VM collected data. CK, EOL, HMs, SG, VS, PS curated the data. KM and PM analysed the data. Authors who verified the data and analyses and had full access to the data were: AKT, EAw, HMs, NW, KM (household surveys); DAn, SAk, TM, KM (hospital data); AKa, AO, ASam, VM, KM (mortality data). KPA and PM led the paper writing with contribution from ASam, KMo MH, DM, DS, PN, RO. AH, AO, ASam, DAn, DM, DS, EAa, KK, KMa, KMo, MH, NW, PBe, PN, PW, RS, SAk, TM, VM reviewed and edited the paper. All authors approved the final version of the manuscript, decided to publish the manuscript, and agreed to be accountable for all aspects of the work.

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Declaration of interests

Some authors of this pilot evaluation previously participated in RTSS malaria vaccine clinical trials as Principal- or co-investigators (Kwaku Poku Asante, Samuel Akech, Abraham Oduro, Titus K. Kwambai, Mary J. Hamel, MD, Nelli Westercamp, PhD, Patricia Njuguna, MD, Prof Daniel Ansong, MD, Simon Kariuki, PhD, Tisungane Mvalo, MBBS, Prof David Schellenberg, PhD, Lucas Otieno, MBChB, Philip Bejon, FMedSci, PhD, Prof Tsiri Agbenvega, PhD , Robert W. Snow, FMedSci, Aaron M. Samuels, MD, Pedro Alonso MD, John Aponte, Bella Ondiegi, Brian Seda, Dorcas Akach, Gordon Orwa, Isabella Nyang'au, Oscar Odunga, Francis Gumba, Jon Juliano) prior to or following WHOs RTSS malaria pilot implementation programme.

Prof Fred Binka was a member of the WHO Global Malaria Programmes Malaria Policy Advisory Committee; Prof Kwadwo Koram was a member of the data safety monitoring board of the RTSS malaria vaccine trials. Dr Pedro Alonso (former Director of WHOs Global Malaria Programme. and Dr Katherine O'Brien (Director of WHO Immunisation, Vaccine and Biologicals Department)

were responsible for overall policy decision-making process for introduction of RTSS malaria vaccines. The authors were not involved in the RTSS vaccine delivery program.

Data sharing
Anonymised data will be made available through Data Compass. Requests for access will be reviewed by a data access committee.

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